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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

JUL - 9 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: FATTY ALCOHOLS: Review of a Developmental Toxicity Study

TO: Margarita Collantes/Bruce Sidwell, PM 53
Reregistration Division

FROM: SanYvette Williams, D.V.M. *2/7/93*
Toxicology Branch II/Section IV (H7509C)
Health Effects Division

THROUGH: Jess Rowland M.S., Acting Section Head *2/7/93*
Toxicology Branch II/Section IV (H7509C)
Health Effects Division
and
Marcia Van Gemert, Ph.D., Branch Chief
Toxicology Branch II (H7509C) *M Van Gemert 2/8/93*
Health Effects Division

EPA IDENTIFICATION #'s: DP Barcode: D186851
Submission: S433662
Case #: 4004
ID#: 79029
MRID #: 426342-01

Action Requested: Review the developmental toxicity study in rat to fulfill the data requirement according to guideline # 83-3a.

Conclusion: A Data Evaluation Report is attached for the submitted study. Pregnant CD rats were administered Fatty Alcohol Blend via gavage at dose levels of 0, 125, 375 or 1000 mg/kg/day on gestational days (GDs) 6-16, inclusively. Compound related maternal toxicity was observed at 1000 mg/kg/day and was manifested as an increased incidence of salivation in dams. Consequently, the NOEL and LOEL for maternal toxicity were 375 and 1000 mg/kg/day, respectively. Developmental toxicity was not observed in this study. Therefore, the NOEL for developmental toxicity was 1000 mg/kg/day (limit dose).

Core Classification: Minimum. This study satisfies the data requirements (83-3a) for a developmental toxicity study in rats and is acceptable for regulatory purposes.



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FINAL

DATA EVALUATION REPORT

FATTY ALCOHOL BLEND

Study Type: Developmental Toxicity

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

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9300 Lee Highway
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Principal Reviewer:

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Date

6/25/93

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Date

6/25/93

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Date

6/25/93

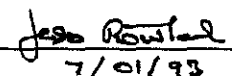
Contract Number: 68D10075
Work Assignment Number: 2-40/1
Clement Number: 202
Project Officer: Caroline Gordon

Guideline Series 83-3: Developmental Toxicity

EPA Reviewer: SanYvette Williams, D.V.M.
Review Section IV, Toxicology Branch II/HED

Signature: 
Date: 6-29-93

EPA Section Head: Jess Rowland, M.S.
Review Section IV, Toxicology Branch II/HED

Signature: 
Date: 7/01/93

DATA EVALUATION REPORT

STUDY TYPE: Developmental toxicity (rat); Guideline Series 83-3 (a)

EPA IDENTIFICATION NUMBERS

DP Barcode: D186851

PC Code: 079029

MRID No.: 426093-01

TEST MATERIAL: Fatty Alcohol Blend

SYNONYM: FAB

SPONSOR: Compliance Services International, Sunnyvale, CA

IRI PROJECT NUMBER: 490327

TESTING FACILITY: Inveresk Research International, Tranent, Scotland

TITLE OF REPORT: Fatty Alcohol Blend; (FAB) Lot No. CSI-91FA01-27:
Teratogenicity Study in Rats

AUTHORS: J.A. Wilson and K.P. Hazelden

REPORT ISSUED: April 29, 1992

CONCLUSIONS: A developmental toxicity study was conducted in which CD rats were administered FAB via gavage at dose levels of 0, 125, 375, or 1000 mg/kg/day on gestational days (GDs) 6-16, inclusively. Compound related maternal toxicity was observed at 1000 mg/kg/day and was manifested as an increased incidence of salivation in dams. Consequently, the NOEL and LOEL for maternal toxicity were 375 and 1000 mg/kg/day, respectively.

Developmental toxicity was not observed in this study. Consequently, the NOEL for developmental toxicity was 1000 mg/kg/day (limit dose).

CORE CLASSIFICATION: Minimum. This study satisfies the data requirements [83-3a] for a developmental toxicity study in rats and is acceptable for regulatory purposes.

Guideline Series 83-3: Developmental Toxicity

A. MATERIALSTest Compound

Purity: Not applicable
 Compositions: Hexanol 0.16%; Octanol 40.7%; Decanol 55.3%;
 Dodecanol 0.42%
 Description: Colorless liquid
 Lot number: CSI-91FA01-27
 Receipt date: October 24, 1991
 Contaminants: Not reported

Vehicle: Corn oil (Safeway Stores, Limited, U.K.)

Test Animals

Species: Rat
 Strain: Crl: CD Sprague-Dawley
 Source: Charles River (UK), Limited, Kent, England
 Age: Approximately 9 weeks upon arrival
 Weight: Approximately 240 g (females) upon arrival
 Males used: Same strain from the same source used as breeders in
 an earlier range-finding study

B. STUDY DESIGN

This study was designed to assess the potential of FAB to cause developmental toxicity in CD® rats when administered daily via gavage from GDs 6 through 16, inclusively.

Mating: Following approximately 4 days of acclimation, females were mated (2 females:1 male) with untreated males until mating was confirmed. Sibling matings were avoided. The day a copulation plug or sperm were observed was designated as GD 0.

Animal husbandry: Food (Rat and Mouse Breeder Diet No. 3 [Expanded] SQC) and municipal tap water were available ad libitum throughout the study. A 12-hour light/dark cycle was maintained. Temperature and humidity ranges were 18-22°C and 40-70%, respectively, with 15-20 air changes per hour.

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Group arrangement: Sperm-positive females were assigned to study groups using a computer-generated randomly sequenced numbering system as follows:

Test Group	Dose Level (mg/kg/day)	Number Assigned per Group
Control	0	25
Low-dose	125	25
Mid-dose	375	25
High-dose	1000	25

Dose administered: Doses were administered daily via gavage from GDs 6 through 16 in a volume of 5 mL/kg of body weight. Individual doses were adjusted daily based on body weight data. Each concentration of dosing solution was prepared separately once prior to dosing and stored at room temperature. Stability, homogeneity, and concentrations of all dosing solutions were determined prior to the initiation of the study. Dosing solutions were said to be stable for 21 days.

Dose rationale: Dose levels were selected based on the results of a preliminary range-finding study (IRI Project No. 490311, Report No. 7768) in which no significant effects on the dams or fetuses were observed at dose levels up to 1000 mg/kg/day.

Observations: Animals were observed twice daily for mortality, moribundity, and clinical signs. Body weight data were recorded on GDs 0, 6, 9, 13, 17, and 20. Food consumption data was recorded daily from GD 3 through the termination of the study. On GD 20, dams were sacrificed by inhalation of CO₂. Examination of the dams at sacrifice included the following:

- Gross pathology of the thoracic and abdominal cavities
- Body weights
- Gravid uterine weight
- Number of corpora lutea
- Number of implantation sites
- Numbers of resorptions and live and dead fetuses

All live fetuses were examined in the following manner:

- Individual fetal weight and sex
- External anomalies

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- Visceral anomalies in one-half the number of fetuses per litter using the method described by Wilson (1965)
- Skeletal anomalies in all remaining fetuses using Alizarin red S.

Statistical analysis: The body weight gain data were analyzed by ANOVA

Regulatory Compliance

- A signed Statement of No Data Confidentiality Claim, dated December 3, 1992, was provided.
- A signed Statement of Compliance with FDA, EPA, OECD, MHW, MAFF, and MITI GLPs, dated October 19, 1992 and December 3, 1992, was provided.
- A signed Quality Assurance Statement, dated October 6, 1992, was provided.

C. RESULTS

Test Material Analysis

Concentration analyses conducted on dosing solutions revealed values from 95% to 105% of target. Data on homogeneity and stability analyses, conducted in an earlier study (IRI Project No. 353278, Report No. 8818), were not provided in this study.

Maternal Toxicity

Mortality: No compound-related mortality was observed. One dam at 1000 mg/kg/day was sacrificed on GD 13 because of poor health condition. Necropsy revealed ruptured esophagus, thick black material in the stomach, and a red mass in the ventral thoracic region; these findings confirmed that death was caused by gavage error.

Abortion: No abortions were reported.

Clinical observations: Compound-related clinical signs were observed at 1000 mg/kg/day. Excess salivation was noted in 16/25 dams (64%) at various intervals following dosing. No such effect was noted in the control and other dose groups. Therefore, this finding was considered to be compound related. Incidental findings noted in one dam of the same group included hunched posture, piloerection, and subsequent loss of food consumption and body weight following dosing on GD 9.

Body weight: No compound-related effects on body weight (data not shown) and weight gain were observed in any dose group. A summary of maternal body weight gain for selected intervals is presented in Table 1. The authors stated that "...the differences in weight gain over the treatment period were not statistically significant." However, no supporting data were presented. Therefore, the reviewers calculated body weight gain for various intervals but did not reanalyze them.

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Food consumption: No compound-related effects on food consumption were observed at any dose level (data not shown).

Necropsy observations: No compound-related necropsy findings were observed. At 1000 mg/kg/day, necropsy of one dam revealed substantial lung damage due to a possible gavage error.

Cesarean section observations: No compound-related effect was observed for any parameter. A summary of cesarean section data is presented in Table 2.

Developmental Toxicity

No compound-related anomalies were observed at any dose level. Incidences of major external and visceral anomalies are presented in Table 3.

External examinations: Major external anomalies included bilateral anophthalmia (1 fetus at 375 mg/kg/day); unilateral anophthalmia (1 fetus at 125 mg/kg/day); and unilateral microphthalmia and retinal fold in left eye (1 fetus from the control group). No minor anomalies were noted.

Visceral examinations: Major visceral anomalies mostly involved the cardiovascular system in addition to hydrocephalus (internal), dilated brain ventricles, and gastroschisis. They were observed in all dose groups but only as single events (Table 3). The most frequently occurring minor anomalies included distension of ureter(s) and/or displaced or not fully descended testis (data not shown). These findings were observed in all dose groups.

Skeletal examinations: No major skeletal anomalies were observed. The most frequently occurring minor anomalies included ribs (13 complete ribs, 14th supernumerary ribs), sternbrae (retarded number of sternbrae), and incomplete ossification of various bones (data not shown). These findings were observed at similar incidences in all dose groups.

D. REVIEWERS' DISCUSSION/CONCLUSIONS

Acceptance Criteria

The reviewers have completed an Acceptance Criteria check list (Attachment I) to be included with the evaluation of the study. Criteria #6 was partially fulfilled; all other criteria were satisfied.

Test Material Analyses

Analyses of concentrations of the test material in the vehicle were within $\pm 5\%$ of the nominal values. The study authors' claim that the compound was stable in the vehicle for 21 days; however, no data were submitted to substantiate this finding. Although the homogeneity analyses were not provided, the concentration analyses conducted on the

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dose solutions indicated that the compound was stable and was homogeneously distributed throughout the dosing suspension.

Maternal Toxicity

Compound-related maternal toxicity was observed at 1000 mg/kg/day. It was manifested as an increased incidence (67%) of salivation in dams following dosing. Although the study authors attributed this finding to the unpleasant odor and taste of the test compound, the food consumption of these dams was unaffected. Therefore, this effect was considered to be compound related. The body weight, weight gain and food consumption were comparable in all dose groups. No other compound-related effects were noted. Consequently, the NOEL and LOEL for maternal toxicity were 375 and 1000 mg/kg/day, respectively.

Developmental Toxicity

No compound-related effects were observed in deaths/resorptions, in altered growth (body weight and ossification), and in anomalies (major and minor). Consequently, the NOEL for developmental toxicity was 1000 mg/kg/day; the LOEL was not determined.

Study/Reporting deficiencies:

Stability and homogeneity analyses data were not submitted.

Pregnancy status was not confirmed (by staining the uteri of apparently nonpregnant animals with ammonium sulfide) to detect early embryo loss.

E. CORE CLASSIFICATION: Minimum

While study and reporting deficiencies (listed in the Reviewer's Discussion) did not impact negatively upon the outcome of the study, they caused it to be classified as Minimum rather than Guideline Data.

Maternal NOEL = 375 mg/kg/day

Maternal LOEL = 1000 mg/kg/day based on increased incidence of salivation during dosing period

Developmental Toxicity NOEL = 1000 mg/kg/day

Developmental Toxicity LOEL = Not determined

F. RISK ASSESSMENT: Not applicable

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TABLE 1. Mean Body Weight Gain (g \pm S.D.)^{a,b}

Dose Group (mg/kg/day)	Prior to Dosing Period (GDs 0-6)	Dosing Period (GDs 6-17)	Post Dosing Period (GDs 17-20)	Entire Gestation Period (GDs 0-20)	Corrected Body Weight Change ^c (GDs 0-20)
0	36.7 \pm 5.4	87.0 \pm 11.9	55.8 \pm 8.7	179.6 \pm 18.6	81.2 \pm 11.7
125	36.9 \pm 7.1	88.6 \pm 11.9	53.5 \pm 8.3	179.0 \pm 18.6	80.9 \pm 18.2
375	35.9 \pm 4.4	84.7 \pm 11.7	53.4 \pm 7.7	174.1 \pm 18.1	72.2 \pm 13.9
1000 ^d	34.4 \pm 7.6	83.0 \pm 14.1	50.7 \pm 9.9	168.1 \pm 22.4	73.9 \pm 18.1

^aData were extracted from study number 490327, Appendices 6 and 8.^bCalculated (but not analyzed) by the reviewers^cCorrected body weight change = (Body weight on GD 20 - body weight on GD 0) - gravid uterus weight^dN=23; one animal was killed due to poor condition and another animal was excluded due to dosing accident.

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TABLE 2. Cesarean Section Observations^a

Parameter	Dose Level (mg/kg/day)			
	0	125	375	1000
No. animals assigned	25	25	25	25
No. animals pregnant	23	24	25	25
Pregnancy rate (%)	92	96	100	100
Maternal wastage				
No. died/nonpregnant	0	0	0	0
No. died/pregnant	0	0	0	1
No. nonpregnant	2	1	0	0
No. aborted	0	0	0	0
Gravid uterine weight (g)	98.4	98.1	101.8	93.8
Litters w/live fetuses	23	24	25	24
Total corpora lutea	403	433	459	425
Corpora lutea/dam	17.5 ± 2.4 ^b	18.0 ± 1.7	18.4 ± 2.1	17.7 ± 2.3
Total implantations	397	427	448	416
Implantations/dam	17.3 ± 2.4	17.8 ± 1.8	17.9 ± 2.3	17.3 ± 2.4
Total live fetuses	379	401	426	389
Live fetuses/dam	16.5 ± 2.5	16.7 ± 2.1	17.0 ± 2.4	16.2 ± 1.9
Total resorptions	18	26	22	27
Early	18	24	17	24
Late	0	2	5	3
Resorptions/dam	0.8 ± 1.1	1.1 ± 1.1	0.9 ± 0.9	1.1 ± 1.0
Total dead fetuses	0	0	0	0
Dead fetuses/dam	0	0	0	0
Mean fetal weight (g)	3.8 ± 0.2	3.7 ± 0.2	3.8 ± 0.2	3.7 ± 0.3
Preimplantation loss (%)	1	1	2	2
Postimplantation loss (%) ^c	5	6	5	6
Sex ratio (% male)	55	52	50	49

^aData were extracted from study number 490327, Table 4 and Appendix 8.^bMean ± S.D.^cCalculated (but not analyzed) by the reviewers

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TABLE 3. Incidences of Major Fetal Anomalies^a

Findings ^b	Dose Level (mg/kg/day)			
	0	125	375	1000
No. fetuses (litters) examined	379 (23)	401 (24)	426 (25)	389 (24)
<u>External Examination</u>				
Bilateral/unilateral anophthalmia	0	1	1	0
Unilateral microphthalmia	1	0	0	0
Retinal fold in left eye	1	0	0	0
Total No. fetuses (litters) with any major external anomalies	1	1	1	0
<u>Visceral Examination</u>				
Hydrocephalus (internal)				
with domed cranium	0	1	0	0
Slight dilatation of lateral brain ventricles	1	0	0	0
Retro-oesophageal aortic arch	0	0	1	0
Interrupted aortic arch with interventricular septal defect	1	0	0	0
Interrupted aortic arch with defective septation of truncus and conus	0	0	0	1
Interventricular septal defect with rudimentary atrio-ventricular valves, reduced left atrium and enlarged right atrium	1	0	0	0
Retro-oesophageal right subclavian artery	0	0	1	0
Gastroschisis	0	0	0	1
Total No. fetuses (litters) with any major visceral anomalies	2 (2)	1	2 (2)	2 (2)
Total No. fetuses (litters) with any major anomalies	3 (3)	2 (2)	2 (2)	2 (2)

^aData were extracted from study number 490327, Tables 5, 6, and Appendix 9.^bMore than one type of anomaly may be found in one fetus.

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ATTACHMENT I

83-3 Teratology Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1. YES Technical form of the active ingredient tested.
2. YES At least 20 pregnant animals/dose group for mice, rats, or hamsters are available. At least 12 pregnant animals/dose group for rabbits are available.
3. YES At the high dose, overt maternal effects such as slight weight loss are reported (or a limit dose is given, 1,000 mg/kg).
- 4.* YES At the low dose, no developmental toxicity is reported.
5. YES Dosing duration is at least during the period of major organogenesis, but may extend up to one day prior to term.
- 6.* Y/N Analysis for test material stability, homogeneity, and concentration in dosing medium.
7. YES Individual daily observations.
8. YES Individual body weights.
9. YES Individual food consumption.
10. YES Necropsy on all animals.
11. YES Individual uterine examination, including numbers of fetal deaths, early and late resorptions, and viable fetuses per sex.
12. YES All ovaries examined to determine number of corpora lutea.
13. YES Individual litter weights and/or individual fetal weights/sex/litter.
14. YES Individual fetal external examination.
15. YES Individual fetal skeletal examination for 1/3 to 1/2 of each litter for rodents and all for rabbits.
16. YES Individual fetal soft tissue examination.

Criteria marked with an * are supplemental, may not be required for every study.



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Chemical: Fatty alcohols (100% C4-C10)

PC Code: 900424

HED File Code 13000 Tox Reviews

Memo Date: 07/09/93

File ID: TX010376

Accession Number: 412-02-0005

HED Records Reference Center
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